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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,266	12/18/2003	Christian Auclair	1417-03	2270

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/740,266	AUCLAIR ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,43-47 and 50* is/are pending in the application.

4a) Of the above claim(s) *1-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-47 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Election/Restrictions

The Election filed on December 4, 2006 in response to the Restriction Requirement of November 27, 2006 has been entered. Applicant's election of a nucleic acid molecule comprising a cDNA of a zyxin gene, a fragment thereof or a complementary sequence has been acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The restriction requirement is therefore deemed to be proper and is made FINAL.

Claims 1-19, 43-47 and 50 currently pending

Claims 1-19 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 43-47 and 50 are currently under consideration.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

A translation of references EP 0821960 and Roy M. Golstyn et al. filed in the information disclosure statement filed 12/18/0003 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

New Rejections Necessitated by Amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-47 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claim 43 has been amended to include the limitation of "a composition consisting essentially of an active agent". While the claims, as originally field, recites a pharmaceutical composition comprising an active agent, a careful review of the specification and claims, as originally filed, does not appear to lend support for the limitation of "consisting essentially of". In the instant case, it is unclear which elements are excluded from the transitional phrase "consisting essentially of" in claim 43. There is no clear definition provided in the specification for ingredients or steps that would materially affect the composition or the method. See *PPG*, 156 F.3d at 1355, 48 USPQ 2d at 1355 for example. Therefore, the "consisting essentially of" language in the claim is being interpreted as "comprising", see the MPEP § 2111.03. Applicant is invited to point to clear support or specific examples of the claimed limitation in the specification as-filed or remove such amendatory language in response to this action.

Claims 43-47 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining

whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims encompass a method of treating a particular tumor comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating or preventing hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies associated with chromosomal anomalies comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. Thus, the claims encompass method of preventing or treating cancer using gene therapy.

Quantity of experimentation

The quantity of experimentation in the areas of gene therapy for cancer and cancer prevention is extremely large given the unpredictability associated with treating a disease by a method of gene therapy, the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

Guidance in the specification and/or Presence of working examples

The specification teaches that pharmaceutical compositions for the treatment or prevention of tumoral pathology comprise an active agent which stabilizes the actin network of the cytoskeleton of a cell, wherein the agent includes, but is not limited to, a zyxin protein, a nucleic acid molecule comprising or constituted of the zyxin gene, a fragment thereof or their complementary sequence, or an antisense nucleic acid thereof, a cell or a set of cells over expressing the zyxin gene or a protein coded for a fragment thereof or an inhibitor of cofilin (page 9, paragraph 0036). The specification further teaches a pharmacological approach for the treatment of cancers by stabilization of the actin network, wherein NIH3T3 and EWS-Fli cells were contacted with dolastin 11 or jasplakinolide and the polymerization of actin was measured by fluorescence (page 30, paragraph 0108-0110). Moreover, the specification provides examples showing that expression of zyxin EWS-FLI cell lines reduce the tumorigenicity of the tumor cells in nude mice (paragraph 0099, Table 1). However, the

specification appears to be silent on the in-vivo efficacy of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. The specification does not show any success in treating a disease by using a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. The specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. Specifically, the specification has not taught an appropriate tested dose for humans, the amount of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, and applicant has not enabled the pharmaceutical composition because it has not been shown that these polynucleotides are capable of functioning as to that which is being disclosed. Therefore, coupled with the unpredictability associated with using polynucleotides for the treatment or prevention of cancer, as underscored by the prior art below, the criticality of providing workable examples in an unpredictable art, such as gene therapy and/or cancer therapy, is required for the practice of the instant invention.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize the unpredictability of treating a disease by a method of gene therapy. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2, *of record*). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-

remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1, *of record*). Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY, *of record*) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82). Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, "...the search for such combinations is a case of trial error for a given cell type" (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, *of record*, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low. More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142, *of record*) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has

not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411, *of record*) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

With regards to preventing cancer, those of skill in the art recognize that reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants arguments pertaining to the previous rejection of Claims 43-49 under 35 U.S.C. 112, first paragraph, scope of enablement to the extent applicable to the instant rejection.

In response to the previous rejection, Applicants assert that the specification clearly discloses a method of treating or preventing hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma, malignant hemopathies associated with chromosomal anomalies of region 7q34/q35 of a zyxin gene. For example, Applicants assert that the specification provides examples showing that expression of zyxin EWS-FLI cell lines reduces the tumorigenicity of the tumor cells in nude mice, that inhibition of zyxin expression in non-tumorigenic NIH3T3 cells leads to the malignant transformation of these cells and that cofilin inhibitors, such as jasplakinolide and dolastatin 11 promotes cytoskeleton development. As such, Applicants assert that these examples clearly provide a link between the effect of malignant transformation and the level of expression of zyxin. In addition, Applicants assert that most of the references cited by the Examiner pertaining to gene therapy were published several years before the time of the inventions and that many successful gene therapy experiments had been conducted in both in vitro and in vivo models since the publication of these articles and the time of the present inventions.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions with respect to the Examples, the Examiner acknowledges and agrees that the specification provides a link between malignant transformation and the level of expression of zyxin. However, the Examiner recognizes that these arguments do not appear to be

commensurate in scope with the instant claims because the claims are drawn to a method of preventing or treating a tumor comprising administering a composition consisting essentially of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence and the specification, as well as the state of the prior art, does not appear to set forth the necessary guidance and grounds for success in arriving at the presently claimed invention. Regarding Applicants arguments pertaining the references supporting the Examiners position that gene therapy is unpredictable, the Examiner acknowledges that some of the articles were published several years prior to the instant filing date. However, the Examiner recognizes that, in view of two articles cited at the time of the invention or after the time of the invention, gene therapy is still unpredictable. Moreover, it is noted that Applicants have stated that "many successful gene therapy experiments had been conducted in both in vitro and in vivo models since the publication of these articles". However, Applicants have not provided any evidence to support this conclusion. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Therefore, NO claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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